FIGURE 1

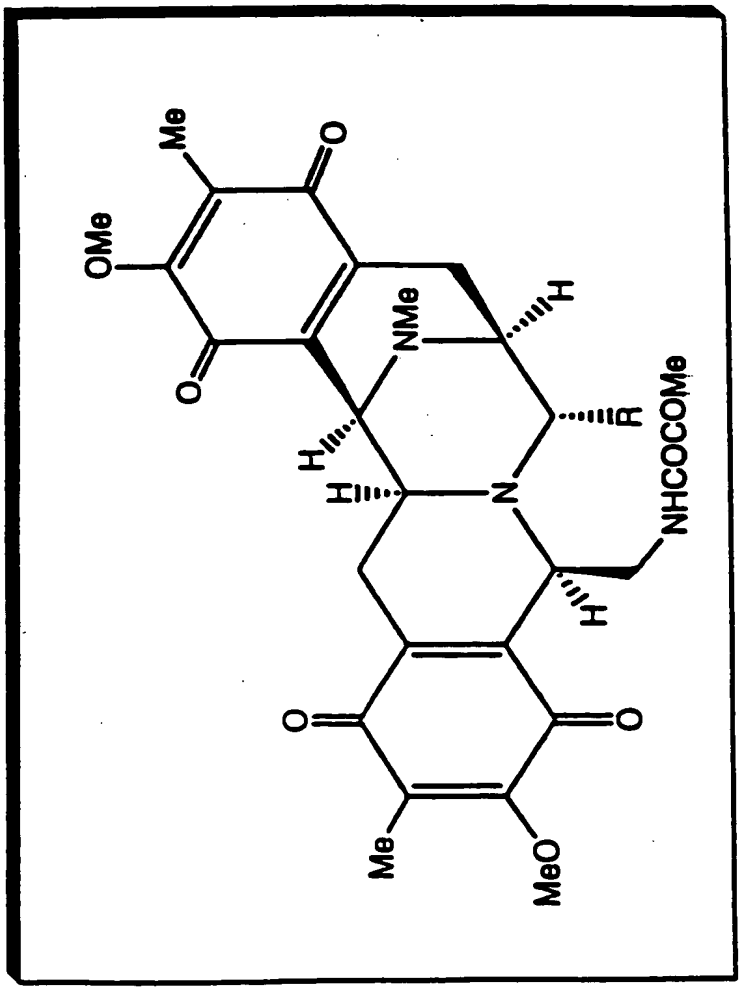


FIGURE 2

Cell lines, IC_{50} (ng/mL)		Synthesis inhibition IC_{50} (μg/mL)	
P 388	0.2	Prot	>1
A 549	0.2		
HT 29	0.5	DNA	0.1
MEL 28	5.0	RNA	0.03
CV-1	1.0		

FIGURE 3

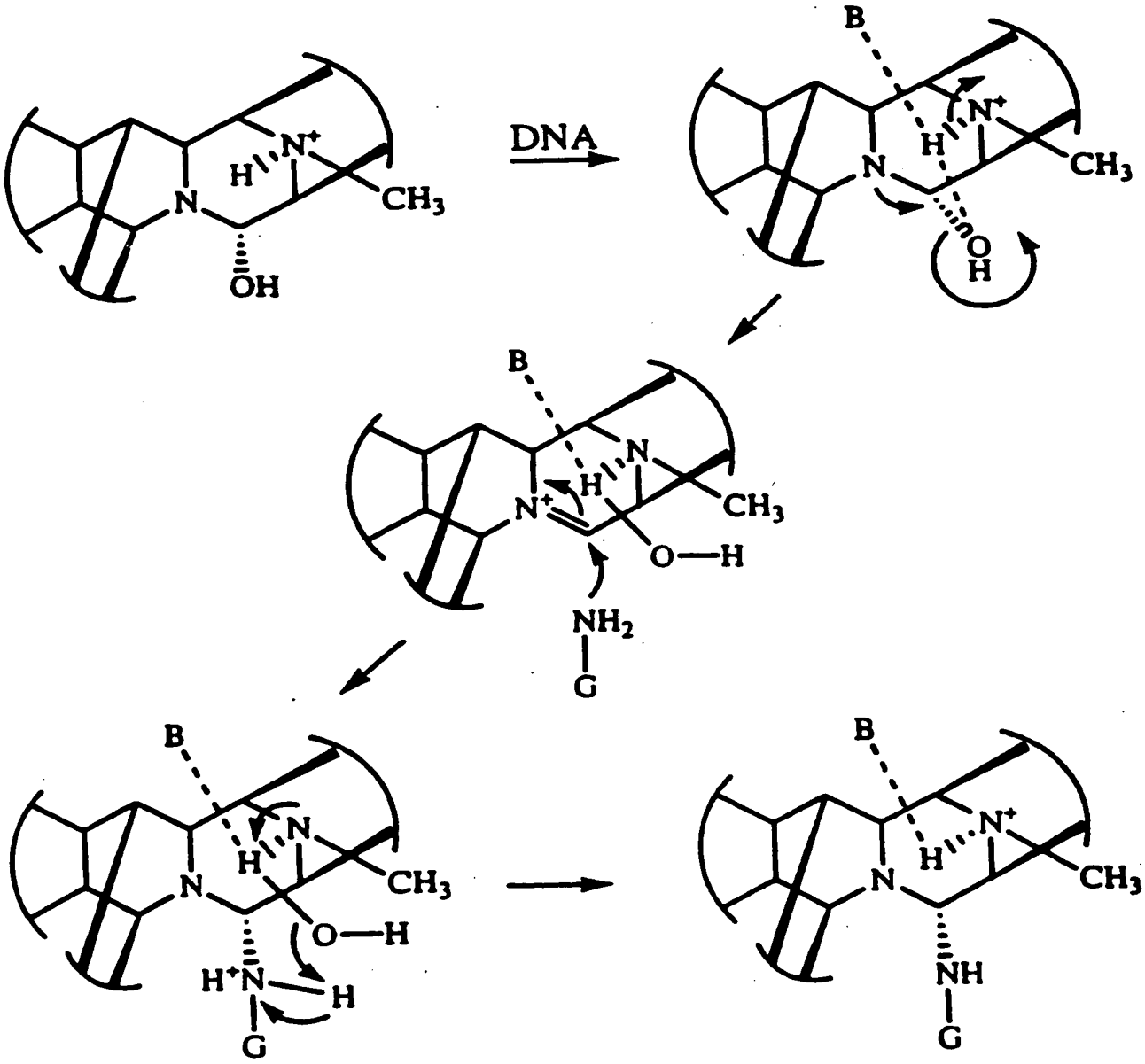
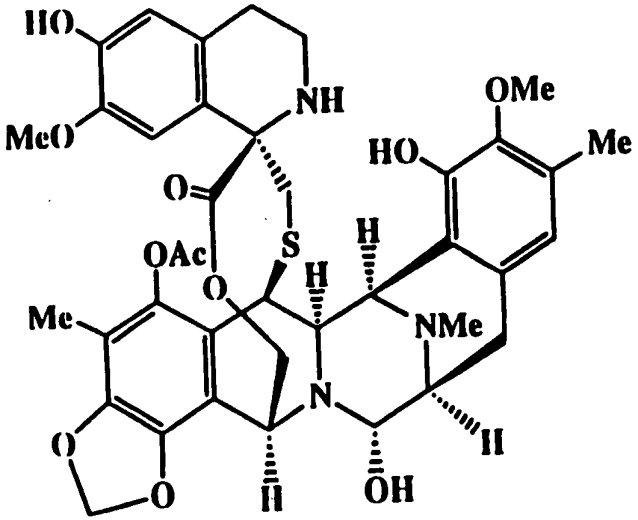
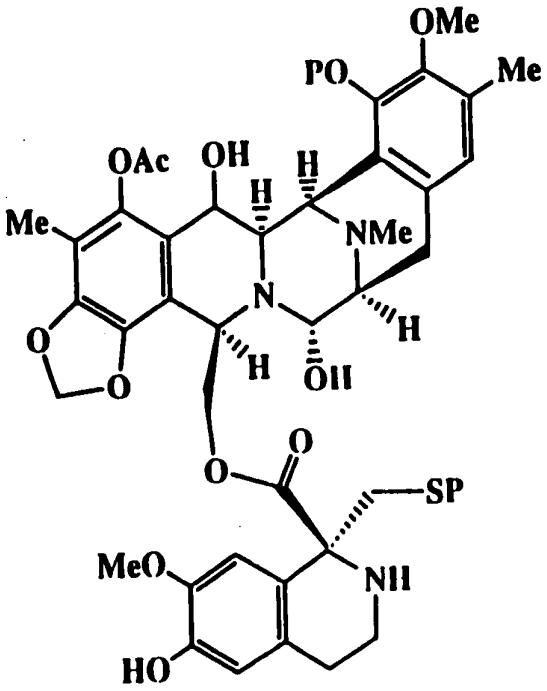
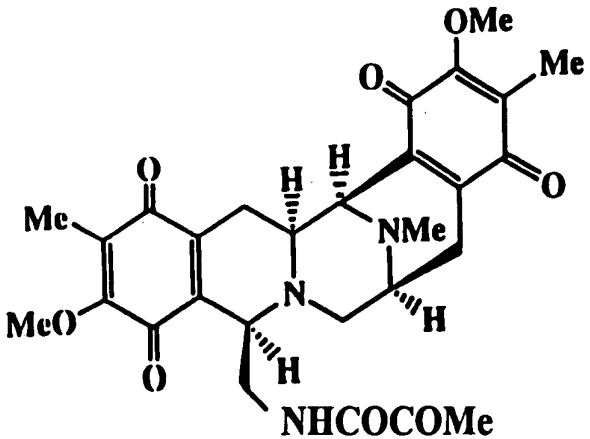


FIGURE 4A



ET 743





Saframycin B

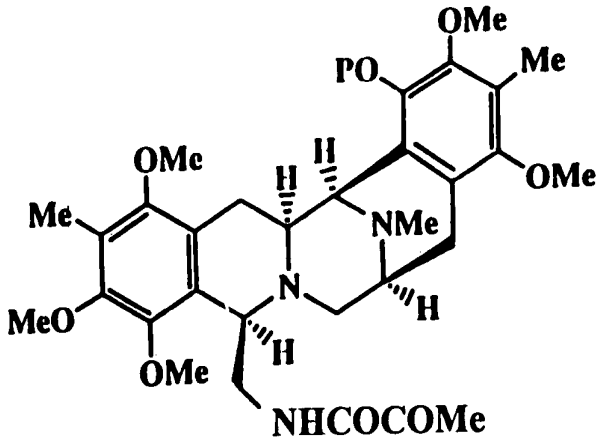
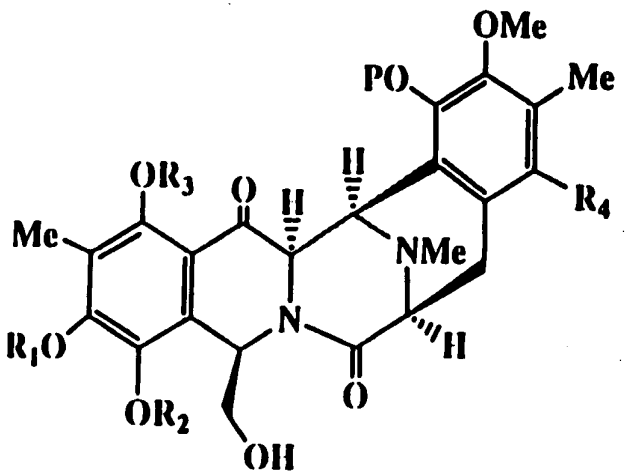
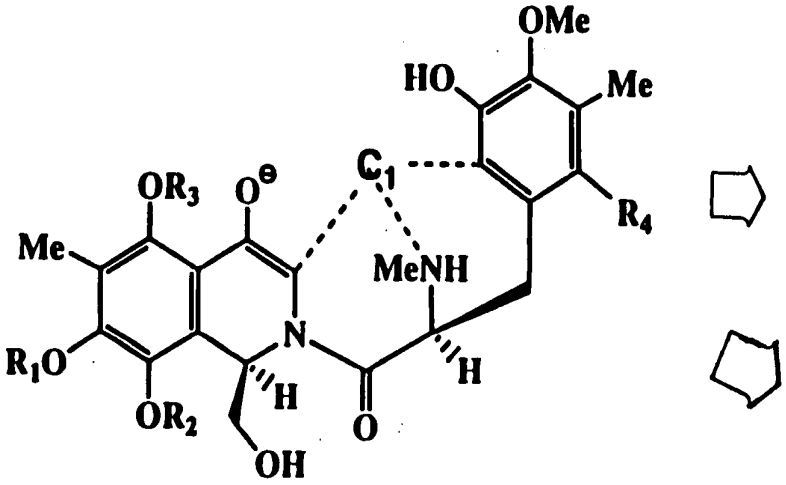


FIGURE 4B

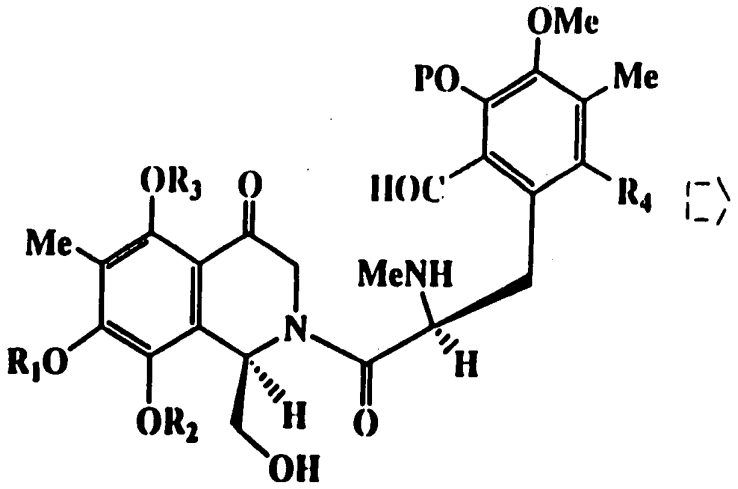


A

B



Strategy A: C_1 insertion, one carbon equivalent,
i.e.: $(RO)_3CH$, $MeOCH(NMe_2)_2$



Strategy B: Mannich-like cyclization

Intermediate for :

<u>Saframycin B</u>: $R_1=R_2=R_3=Me$, $R_4=OMe$

<u>ET 743</u>: R_1, $R_2=-CH_2-$, $R_3=Ac$, $R_4=H$

FIGURE 4C

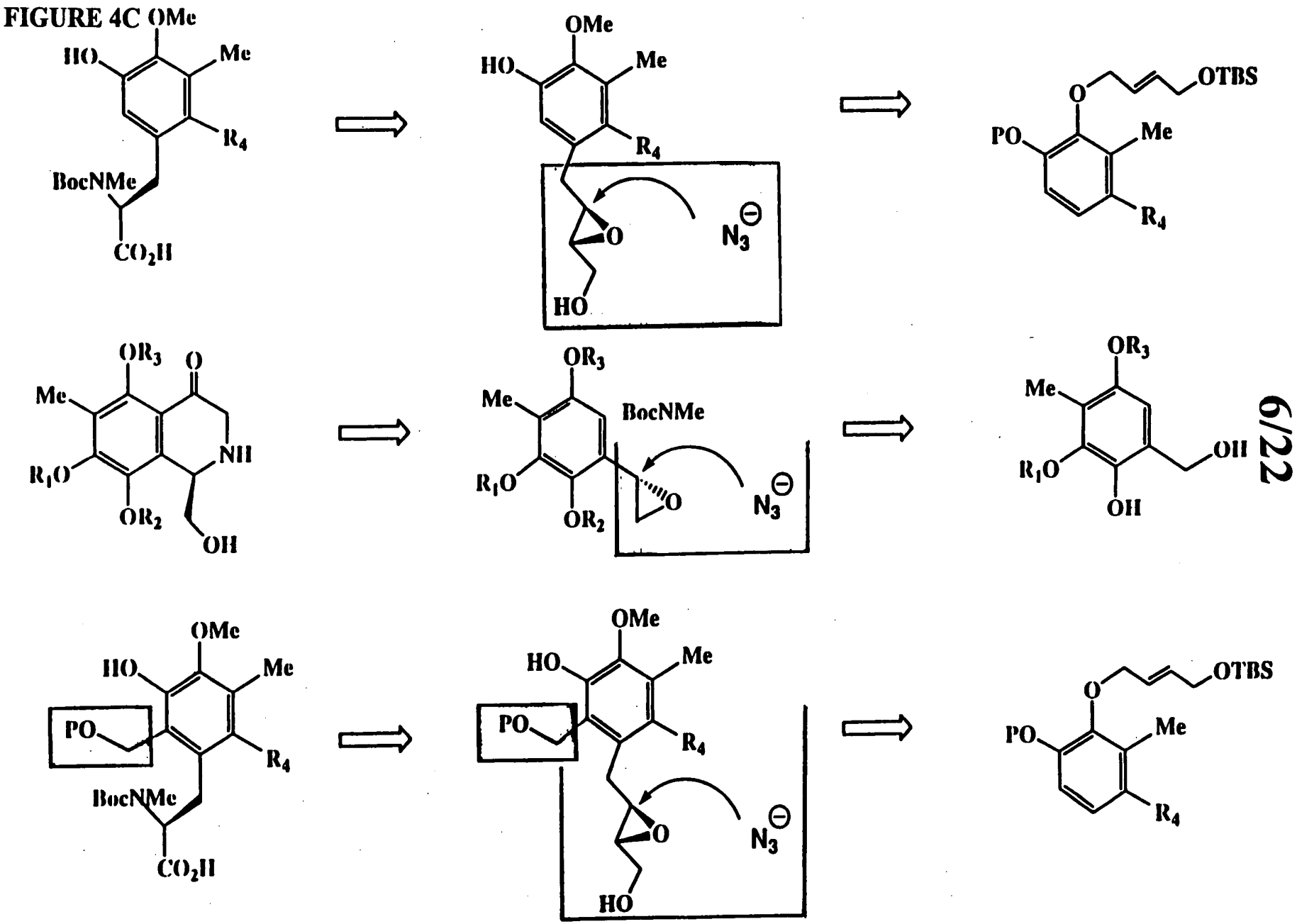
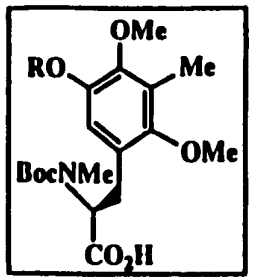
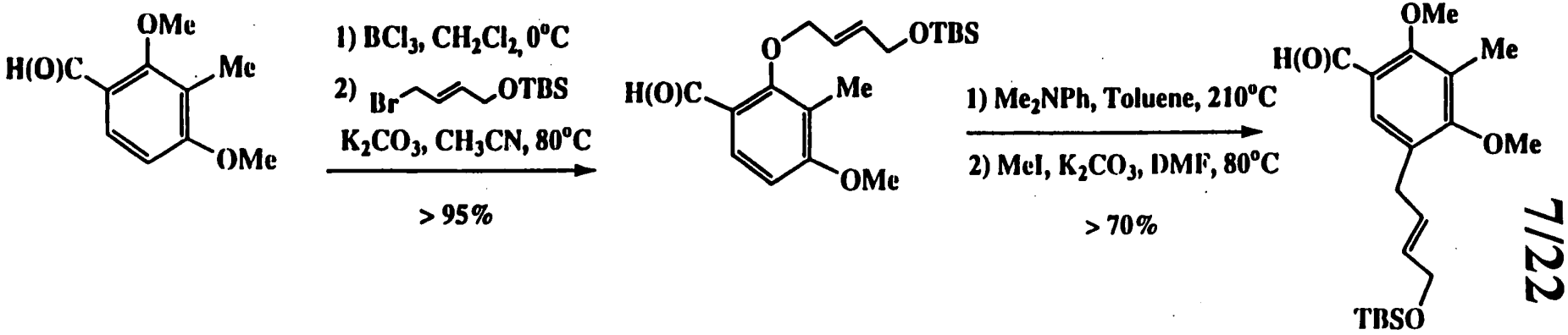


FIGURE 5A


OMe
RO
Me
OMe
BocNMe
CO_2H


OMe
H(O)C
Me
OMe
1) BCl_3, CH_2Cl_2, 0°C
2) Br OTBS
K_2CO_3, CH_3CN, 80°C
> 95%
O
OTBS
H(O)C
Me
OMe
1) Me_2NPh, Toluene, 210°C
2) MeI, K_2CO_3, DMF, 80°C
> 70%
OMe
H(O)C
Me
OMe
TBSO

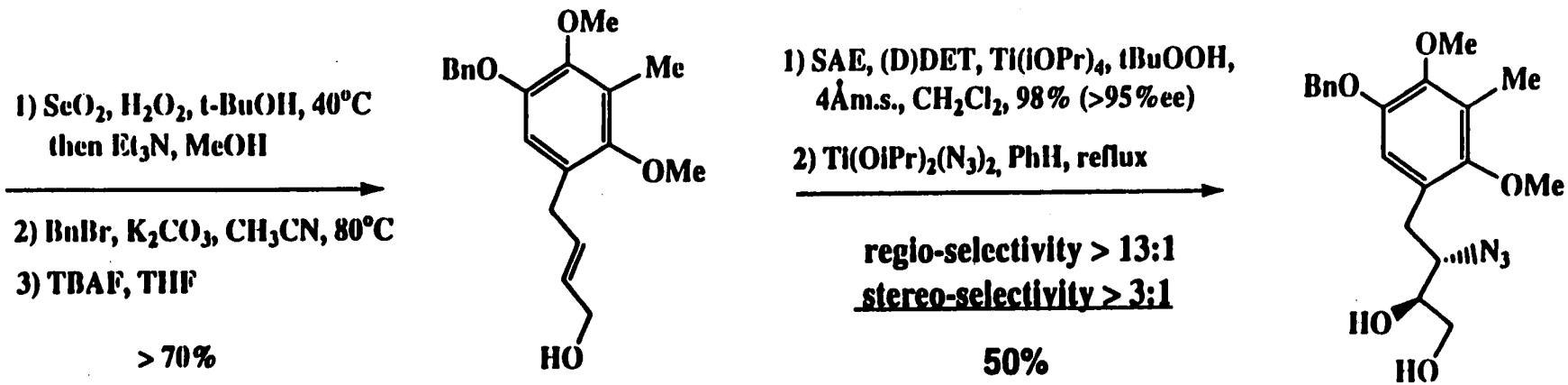

1) SeO_2, H_2O_2, t-BuOH, 40°C
then Et_3N, MeOH
2) BnBr, K_2CO_3, CH_3CN, 80°C
3) TBAF, THF
> 70%
OMe
BnO
Me
OMe
HO
1) SAE, (D)DET, $Ti(iOPr)_4$, tBuOOH,
4Åm.s., CH_2Cl_2, 98% (>95%ee)
2) $Ti(OiPr)_2(N_3)_2$, PhH, reflux
regio-selectivity > 13:1
stereo-selectivity > 3:1
50%
OMe
BnO
Me
OMe
N_3
HO
HO

FIGURE 5B

High regioselectivity and unexpected low stereoselectivity for the azide-opening step:

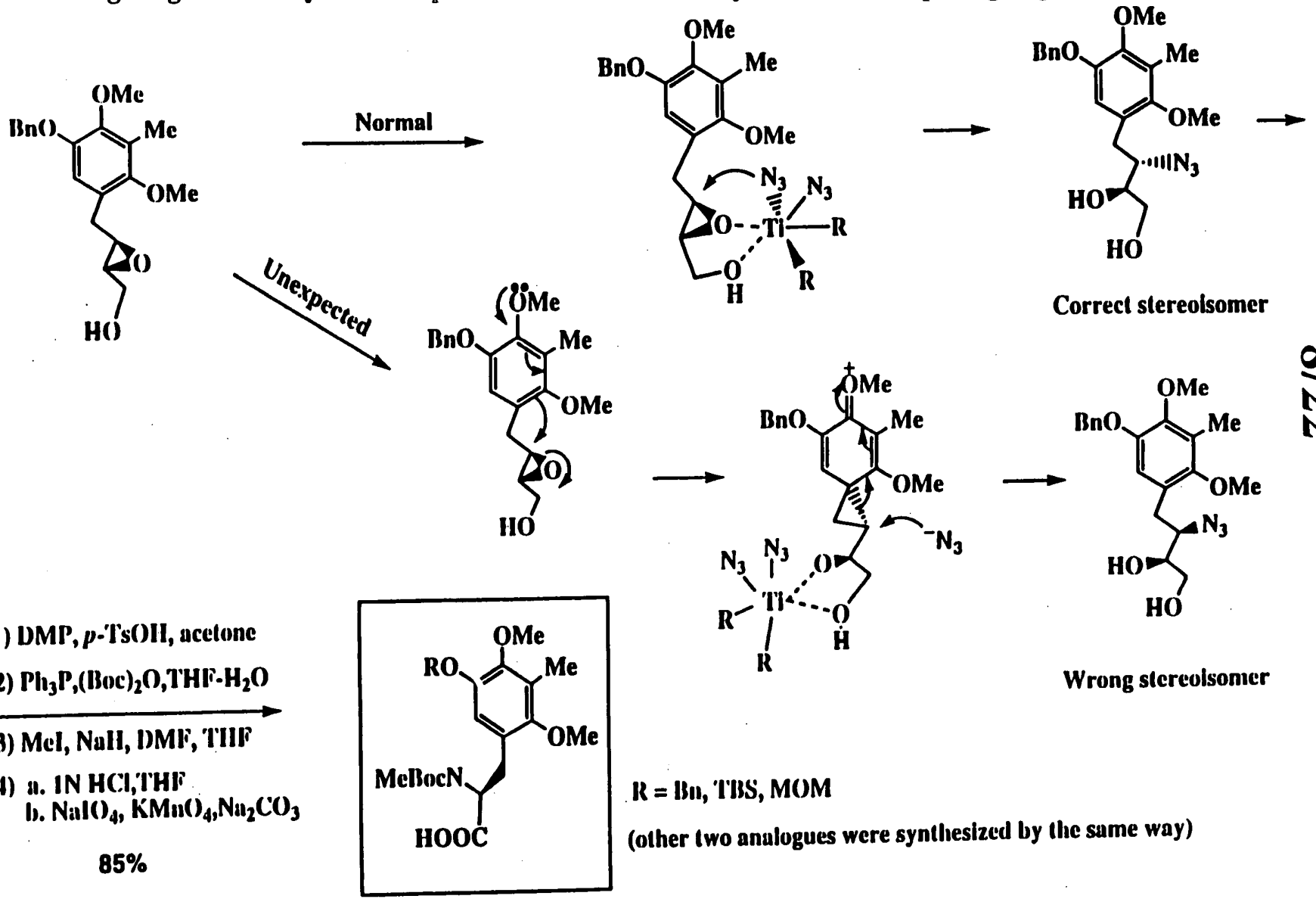


FIGURE 6

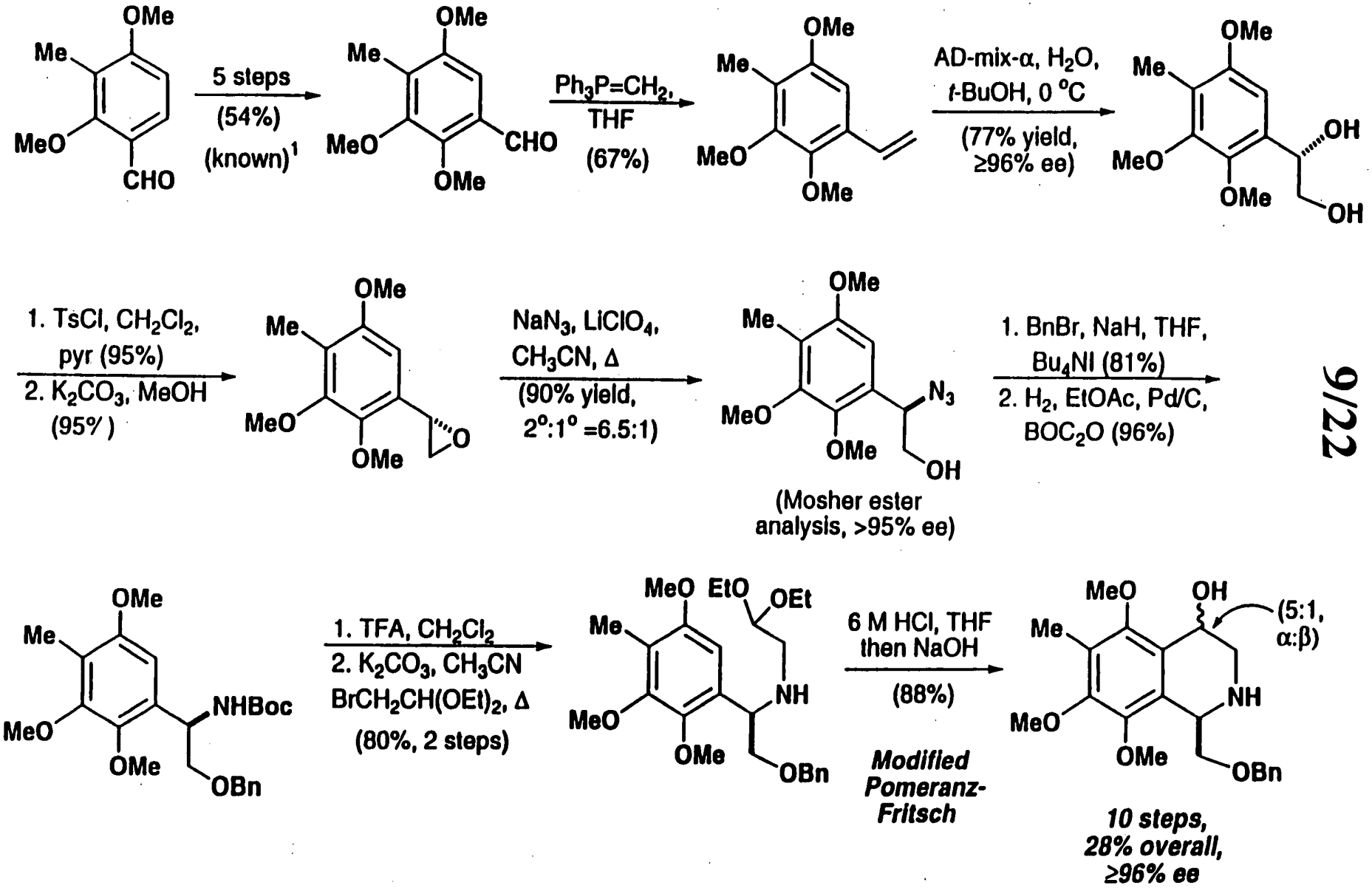
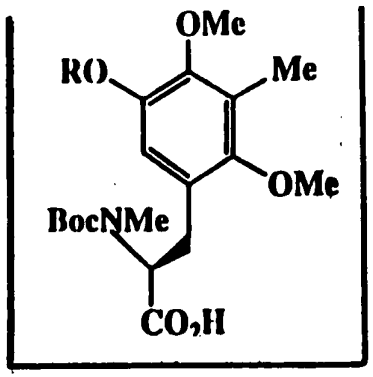

OMe
Me
MeO
CHO
5 steps
(54%)
(known)[1]
CHO
Ph3P=CH2,
THF
(67%)
AD-mix-α, H2O,
t-BuOH, 0 °C
(77% yield,
≥96% ee)
OH
OH
1. TsCl, CH2Cl2,
pyr (95%)
2. K2CO3, MeOH
(95%)
NaN3, LiClO4,
CH3CN, Δ
(90% yield,
2°:1° =6.5:1)
N3
1. BnBr, NaH, THF,
Bu4NI (81%)
2. H2, EtOAc, Pd/C,
BOC2O (96%)
(Mosher ester
analysis, >95% ee)
NHBoc
OBn
1. TFA, CH2Cl2
2. K2CO3, CH3CN
BrCH2CH(OEt)2, Δ
(80%, 2 steps)
MeO EtO
OEt
NH
6 M HCl, THF
then NaOH
(88%)
Modified
Pomeranz-
Fritsch
(5:1,
α:β)
10 steps,
28% overall,
≥96% ee

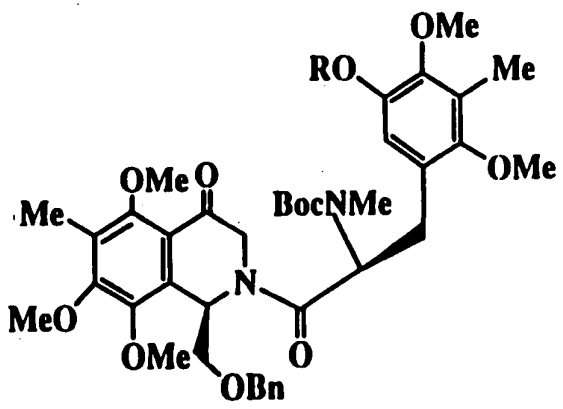
FIGURE 7A



1) BOPCl, Et_3N, CH_2Cl_2

2) Dess-Martin P., CH_2Cl_2

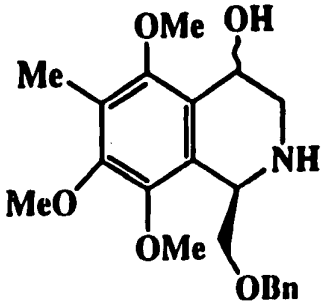
60%



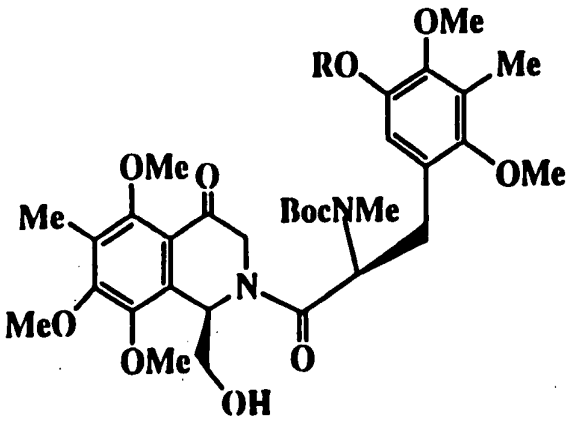
R = Bn, TBS, MOM

H_2, Pd/C, EtOAc

or TBAF, THF



4:1 diastereomers



R = H, MOM

$TFA\text{-}CH_2Cl_2$

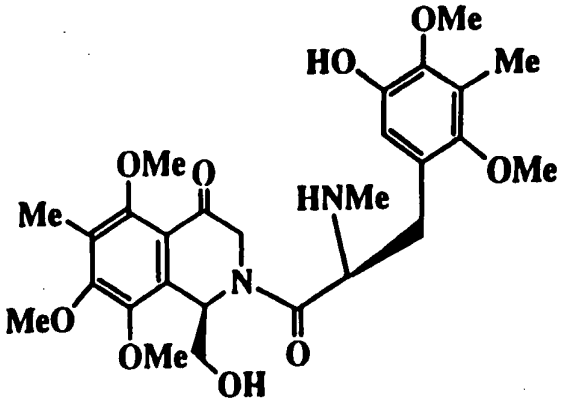
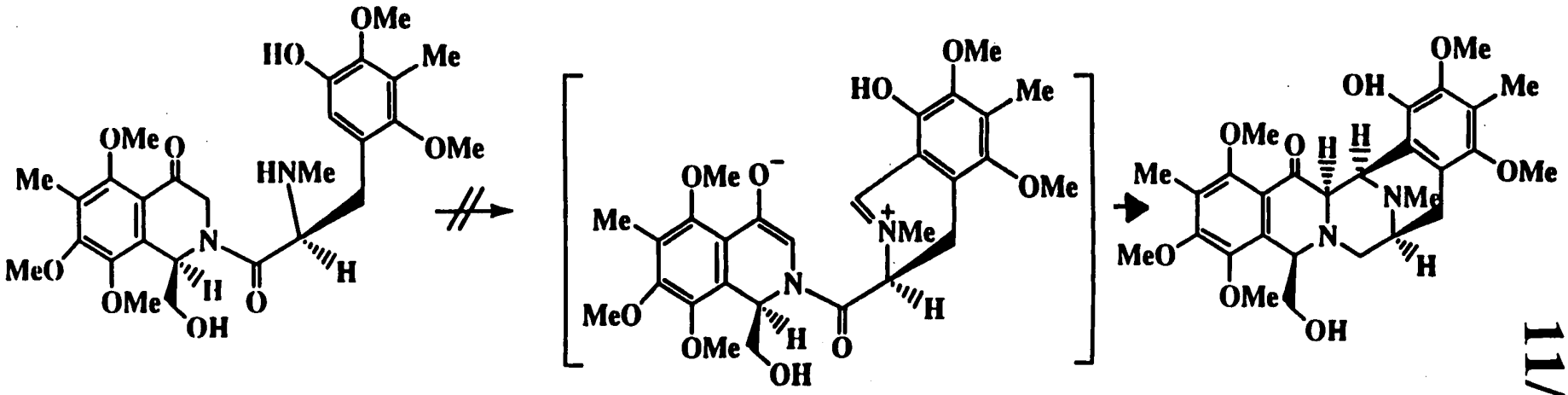


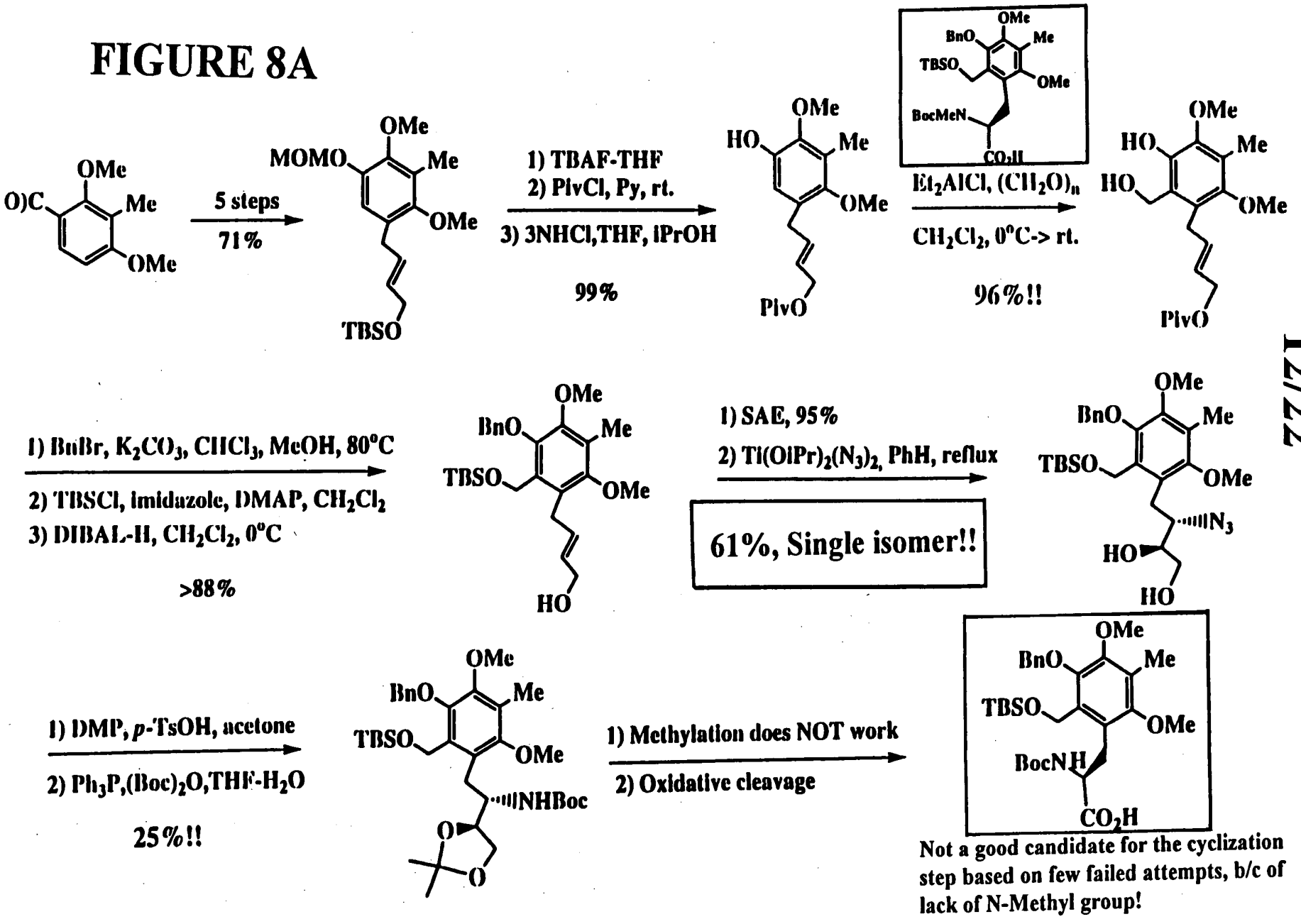
FIGURE 7B



Compound A

Cyclization Conditions:	Product:
> $CH(OMe)_3$, $BF_3{\cdot}Et_2O$, reflux	-
> $CH(OMe)_3$, HCl or CH_3SO_3H, r.t. or heat	-
> Cl_2CHOCH_3, $TiCl_4$, CH_2Cl_2, 0°C-> reflux	-
> Acetic formyl anhydride, CH_2Cl_2, $POCl_3$, DMF	-
> $CH(OMe)_3$, polyphosphoric acid, reflux	-
> *t*-BuOCH$(NMe_2)_2$, toluene, r.t. or reflux	compound A

FIGURE 8A



Not a good candidate for the cyclization step based on few failed attempts, b/c of lack of N-Methyl group!

FIGURE 8B

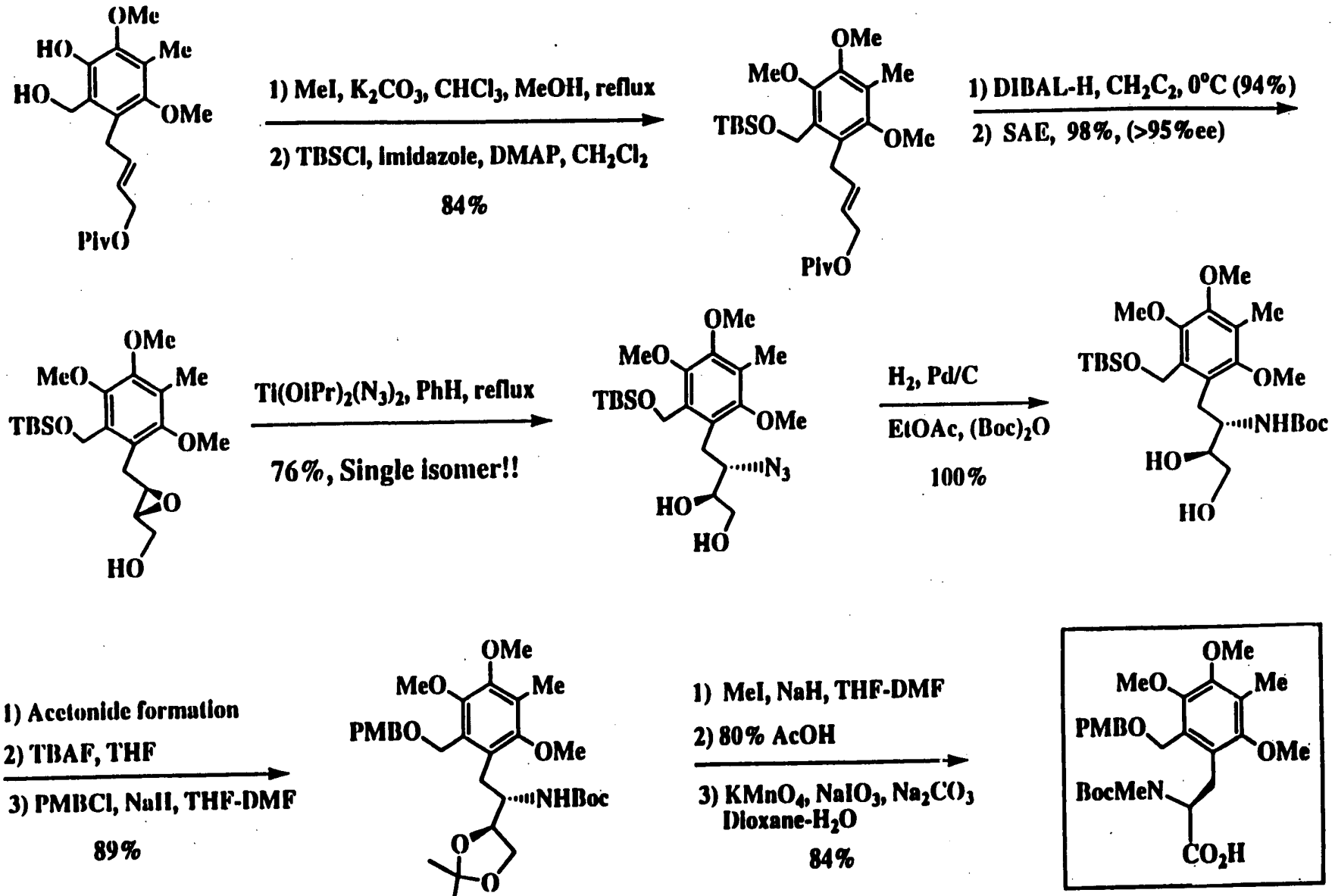
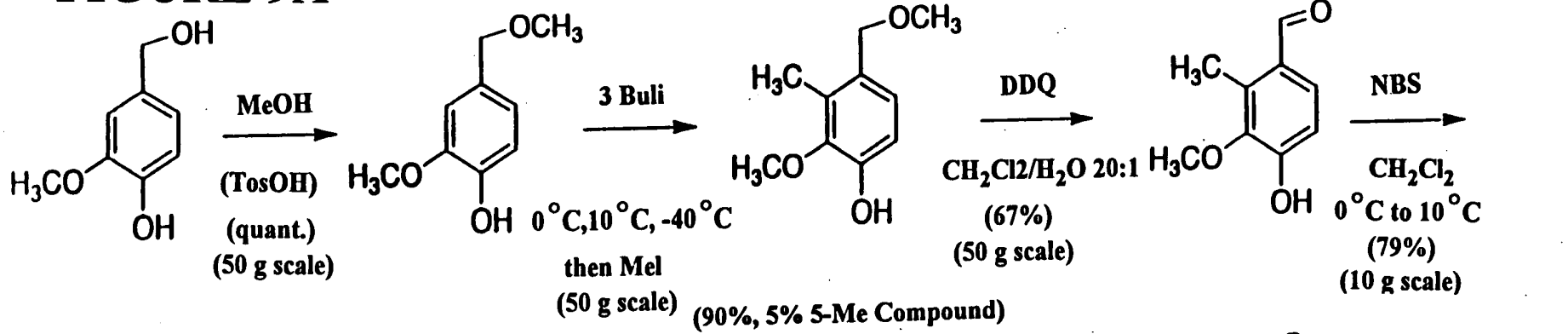
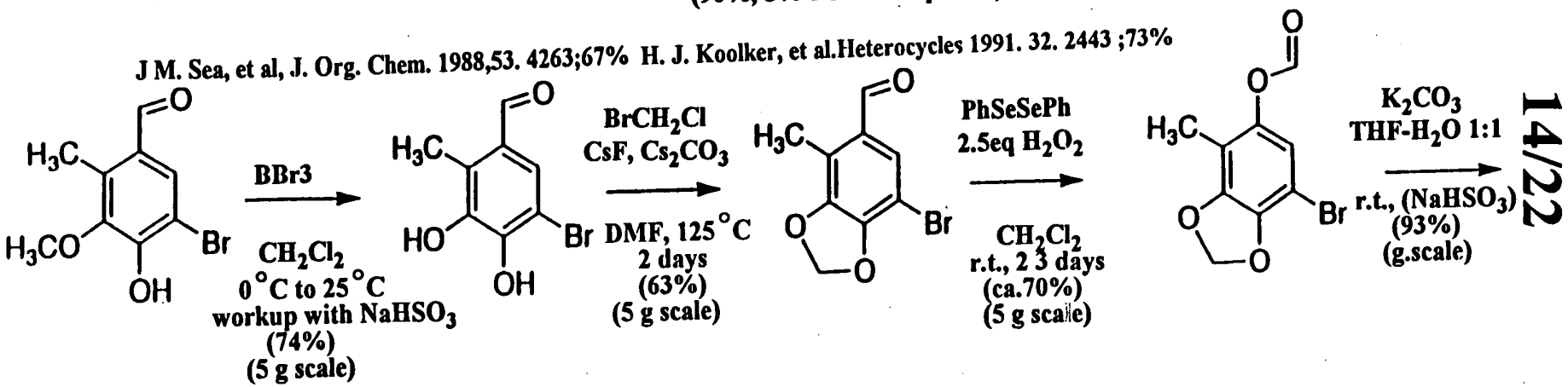

OMe
HO
Me
HO
OMe
PivO
1) MeI, K_2CO_3, $CHCl_3$, MeOH, reflux
2) TBSCl, Imidazole, DMAP, CH_2Cl_2
84%
OMe
MeO
Me
TBSO
OMe
PivO
1) DIBAL-H, CH_2C_2, 0°C (94%)
2) SAE, 98%, (>95%ee)
OMe
MeO
Me
TBSO
OMe
HO
$Ti(OiPr)_2(N_3)_2$, PhH, reflux
76%, Single isomer!!
OMe
MeO
Me
TBSO
OMe
N_3
HO
HO
H_2, Pd/C
EtOAc, $(Boc)_2O$
100%
OMe
MeO
Me
TBSO
OMe
NHBoc
HO
HO
1) Acetonide formation
2) TBAF, THF
3) PMBCl, NaH, THF-DMF
89%
OMe
MeO
Me
PMBO
OMe
NHBoc
O
O
1) MeI, NaH, THF-DMF
2) 80% AcOH
3) $KMnO_4$, $NaIO_3$, Na_2CO_3
Dioxane-H_2O
84%
OMe
MeO
Me
PMBO
OMe
BocMeN
CO_2H

FIGURE 9A



J M. Sea, et al, J. Org. Chem. 1988,53. 4263;67% H. J. Koolker, et al.Heterocycles 1991. 32. 2443 ;73%



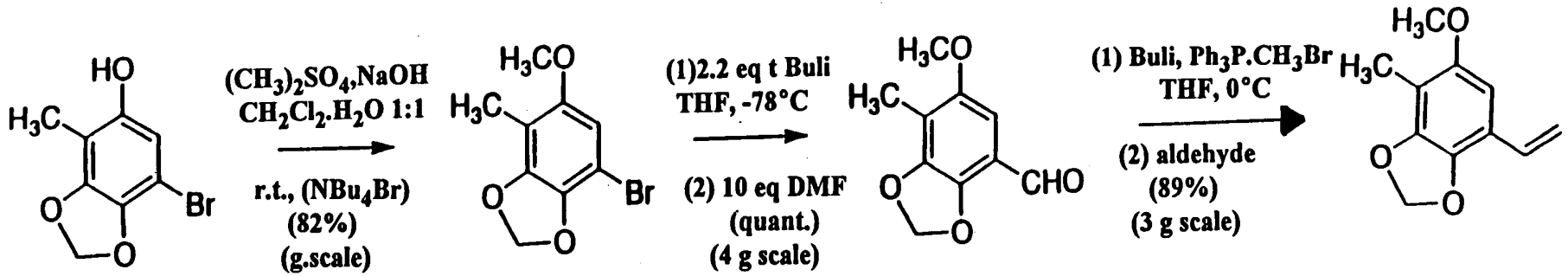


FIGURE 9B

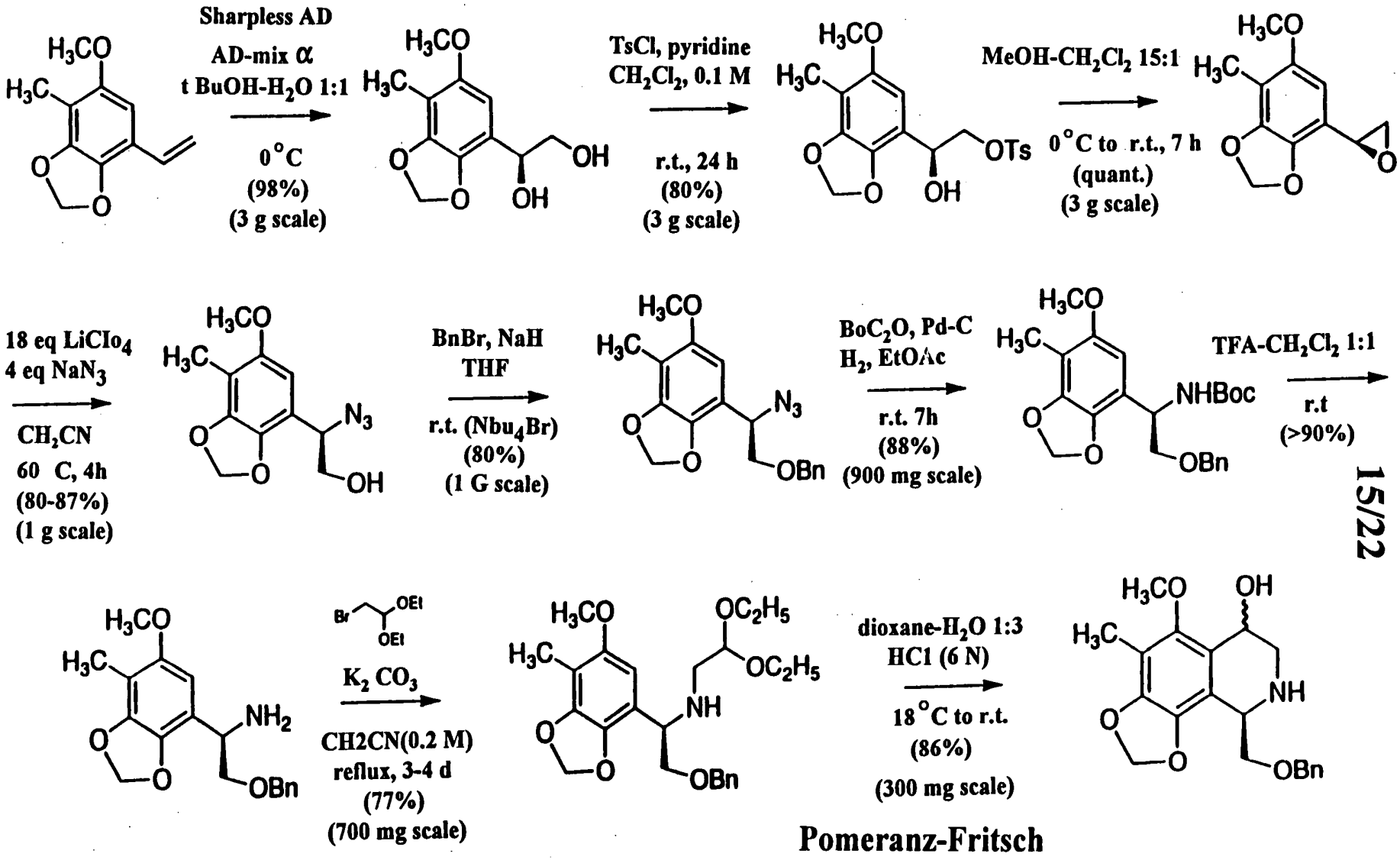
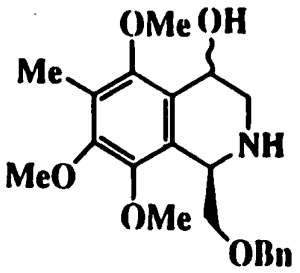
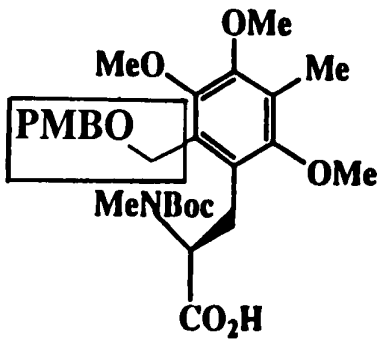

Sharpless AD
AD-mix α
t BuOH-H2O 1:1
0°C
(98%)
(3 g scale)
TsCl, pyridine
CH2Cl2, 0.1 M
r.t., 24 h
(80%)
(3 g scale)
MeOH-CH2Cl2 15:1
0°C to r.t., 7 h
(quant.)
(3 g scale)
18 eq LiClO4
4 eq NaN3
CH2CN
60 C, 4h
(80-87%)
(1 g scale)
BnBr, NaH
THF
r.t. (Nbu4Br)
(80%)
(1 G scale)
BoC2O, Pd-C
H2, EtOAc
r.t. 7h
(88%)
(900 mg scale)
TFA-CH2Cl2 1:1
r.t
(>90%)
K2 CO3
CH2CN(0.2 M)
reflux, 3-4 d
(77%)
(700 mg scale)
dioxane-H2O 1:3
HCl (6 N)
18°C to r.t.
(86%)
(300 mg scale)
Pomeranz-Fritsch

FIGURE 10A



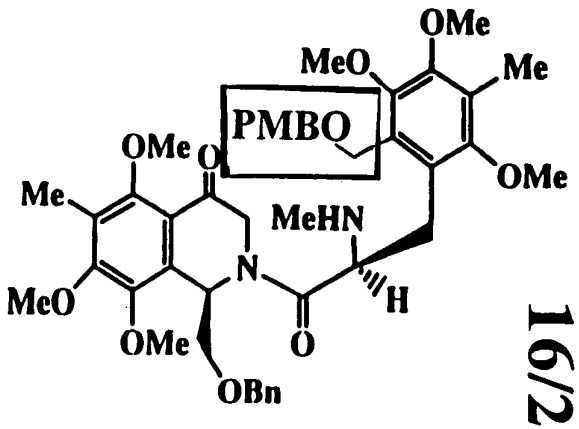
4:1 diastereomers



1) BOPCl, Et_3N, CH_2Cl_2

2) Dess-Martin Oxidation

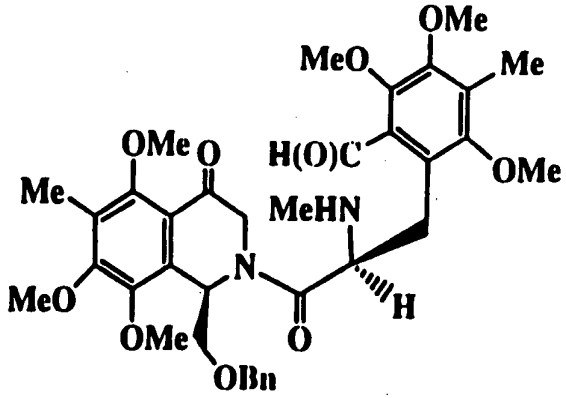
-50%



1) DDQ, CH_2Cl_2, H_2O

2) NMO, TPAP, 4 Å m.s., CH_2Cl_2

-70%



Homochiral product !

FIGURE 10B

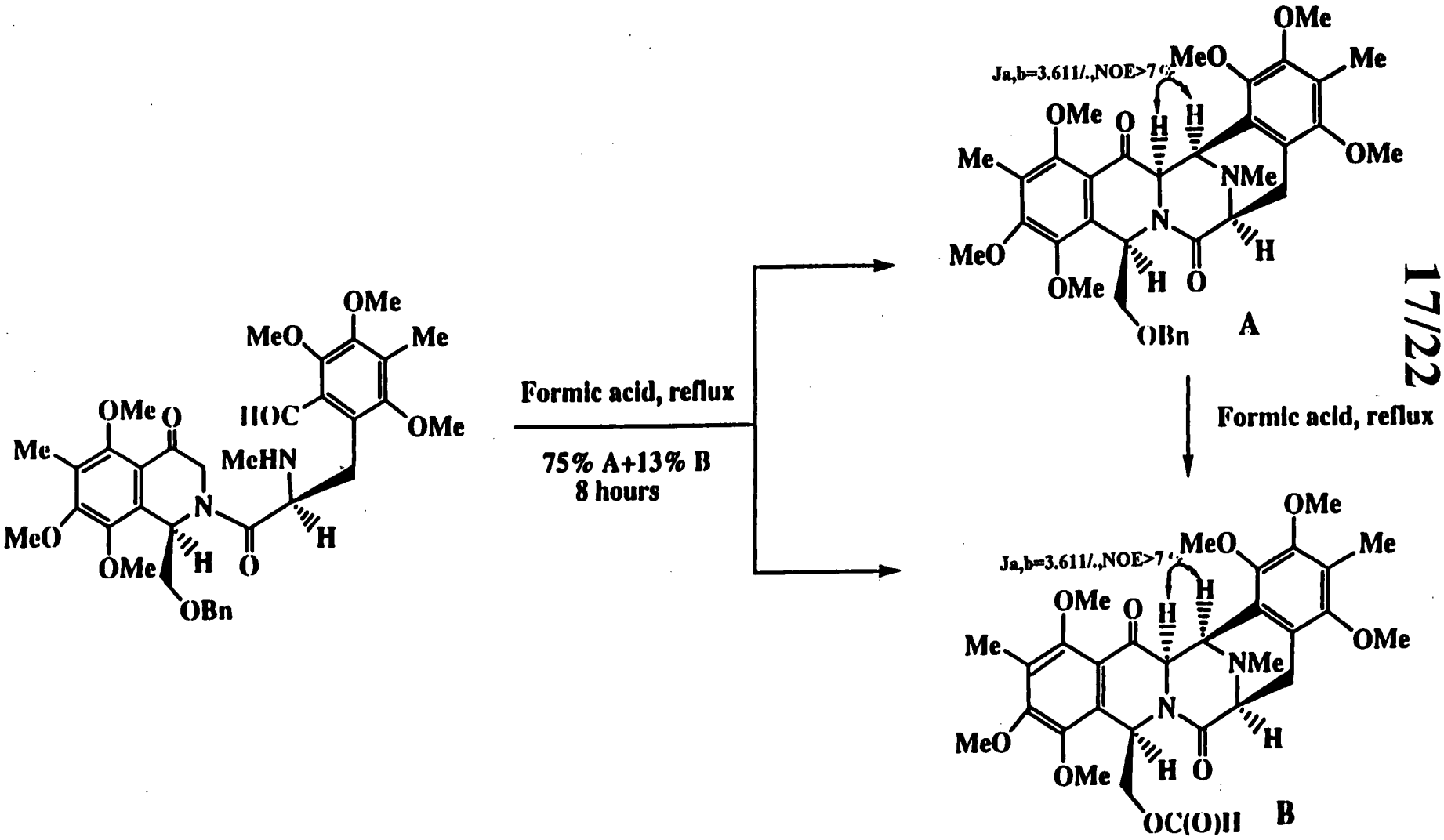

OMe
MeO
Me
HOC
OMe
MeHN
Me
N
MeO
OMe
H
O
H
OBn
Formic acid, reflux
75% A+13% B
8 hours
Ja,b=3.611/.,NOE>7
OMe
MeO
Me
OMe
O
H
H
Me
NMe
OMe
N
MeO
H
OMe
H
O
OBn
A
Formic acid, reflux
Ja,b=3.611/.,NOE>7
OMe
MeO
Me
OMe
O
H
H
Me
NMe
OMe
N
MeO
H
OMe
H
O
OC(O)H
B

FIGURE 11

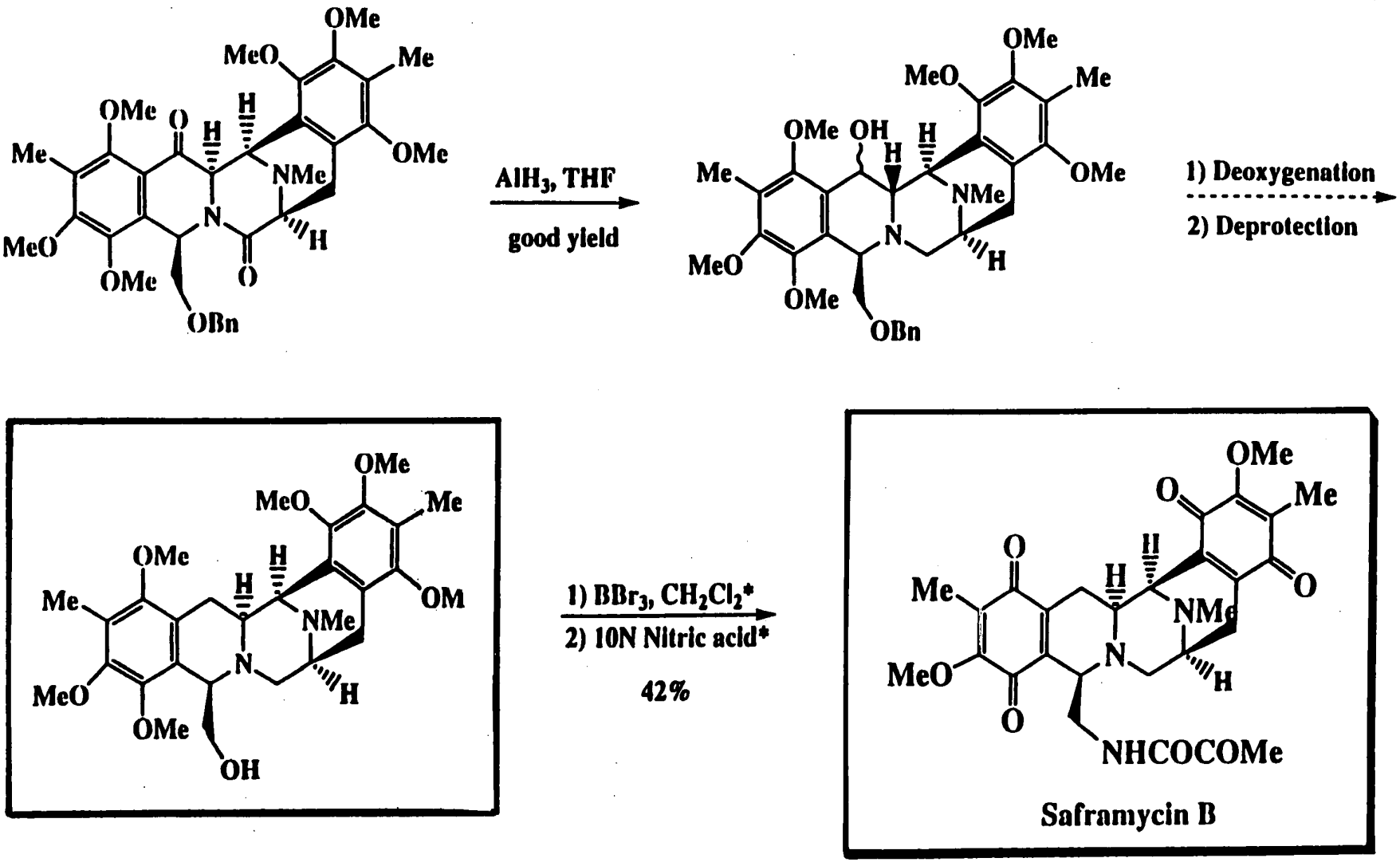

OMe
MeO
Me
OMe
O
H
Me
NMe
OMe
N
MeO
H
OMe
O
OBn
AlH3, THF
good yield
OMe
OH
1) Deoxygenation
2) Deprotection
OM
1) BBr3, CH2Cl2*
2) 10N Nitric acid*
42%
NHCOCOMe
Saframycin B

FIGURE 12

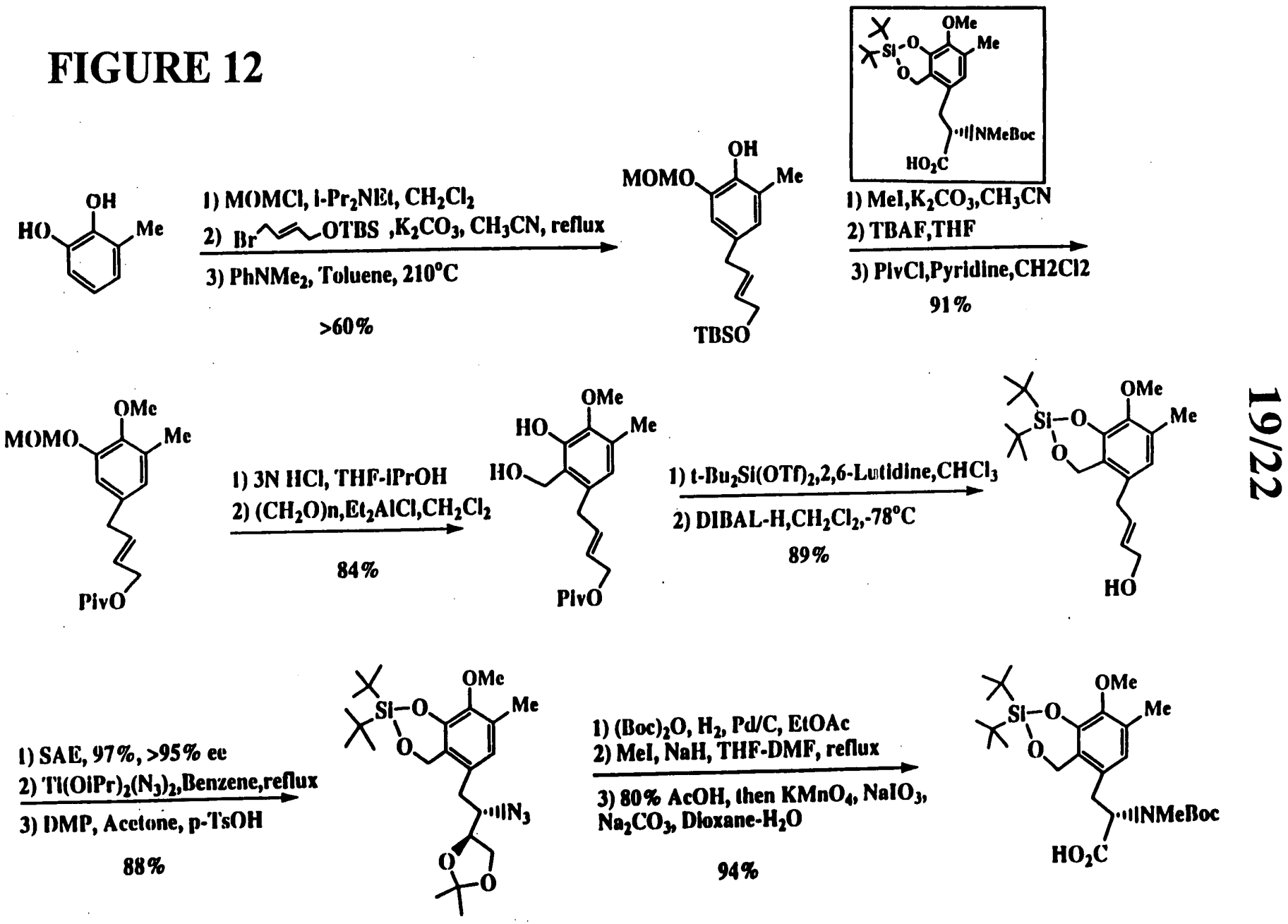

1) MOMCl, i-Pr2NEt, CH2Cl2
2) Br OTBS ,K2CO3, CH3CN, reflux
3) PhNMe2, Toluene, 210°C
>60%
1) MeI,K2CO3,CH3CN
2) TBAF,THF
3) PivCl,Pyridine,CH2Cl2
91%
1) 3N HCl, THF-iPrOH
2) (CH2O)n,Et2AlCl,CH2Cl2
84%
1) t-Bu2Si(OTf)2,2,6-Lutidine,CHCl3
2) DIBAL-H,CH2Cl2,-78°C
89%
1) SAE, 97%, >95% ee
2) Ti(OiPr)2(N3)2,Benzene,reflux
3) DMP, Acetone, p-TsOH
88%
1) (Boc)2O, H2, Pd/C, EtOAc
2) MeI, NaH, THF-DMF, reflux
3) 80% AcOH, then KMnO4, NaIO3, Na2CO3, Dioxane-H2O
94%

FIGURE 13

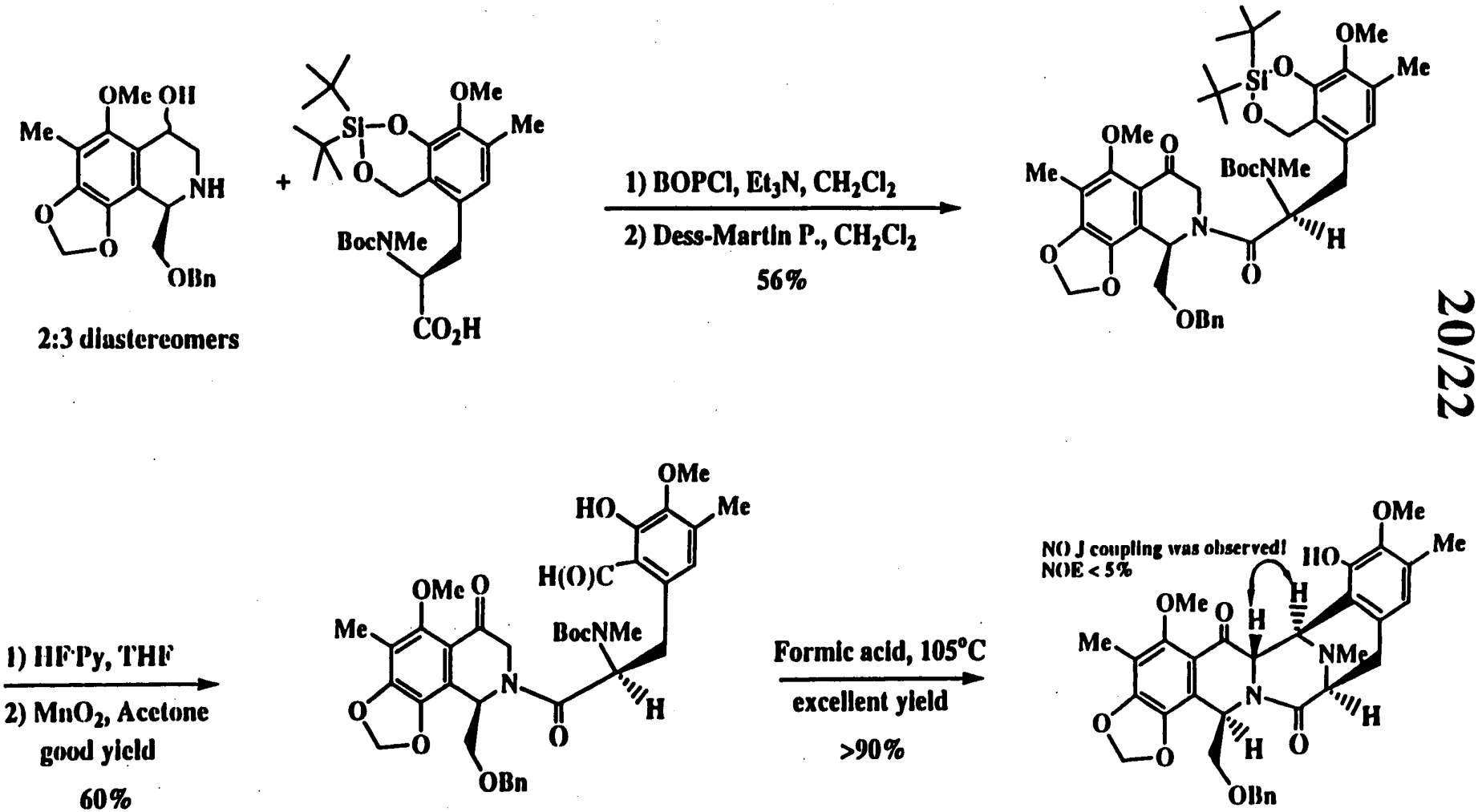

OMe OH
Me
NH
O
O
OBn
2:3 diastereomers
+
Si
O
OMe
Me
BocNMe
CO2H
1) BOPCl, Et3N, CH2Cl2
2) Dess-Martin P., CH2Cl2
56%
OMe
Me
BocNMe
N
O
H
1) HF·Py, THF
2) MnO2, Acetone
good yield
60%
HO
H(O)C
Formic acid, 105°C
excellent yield
>90%
NO J coupling was observed!
NOE < 5%
NMe

FIGURE 14

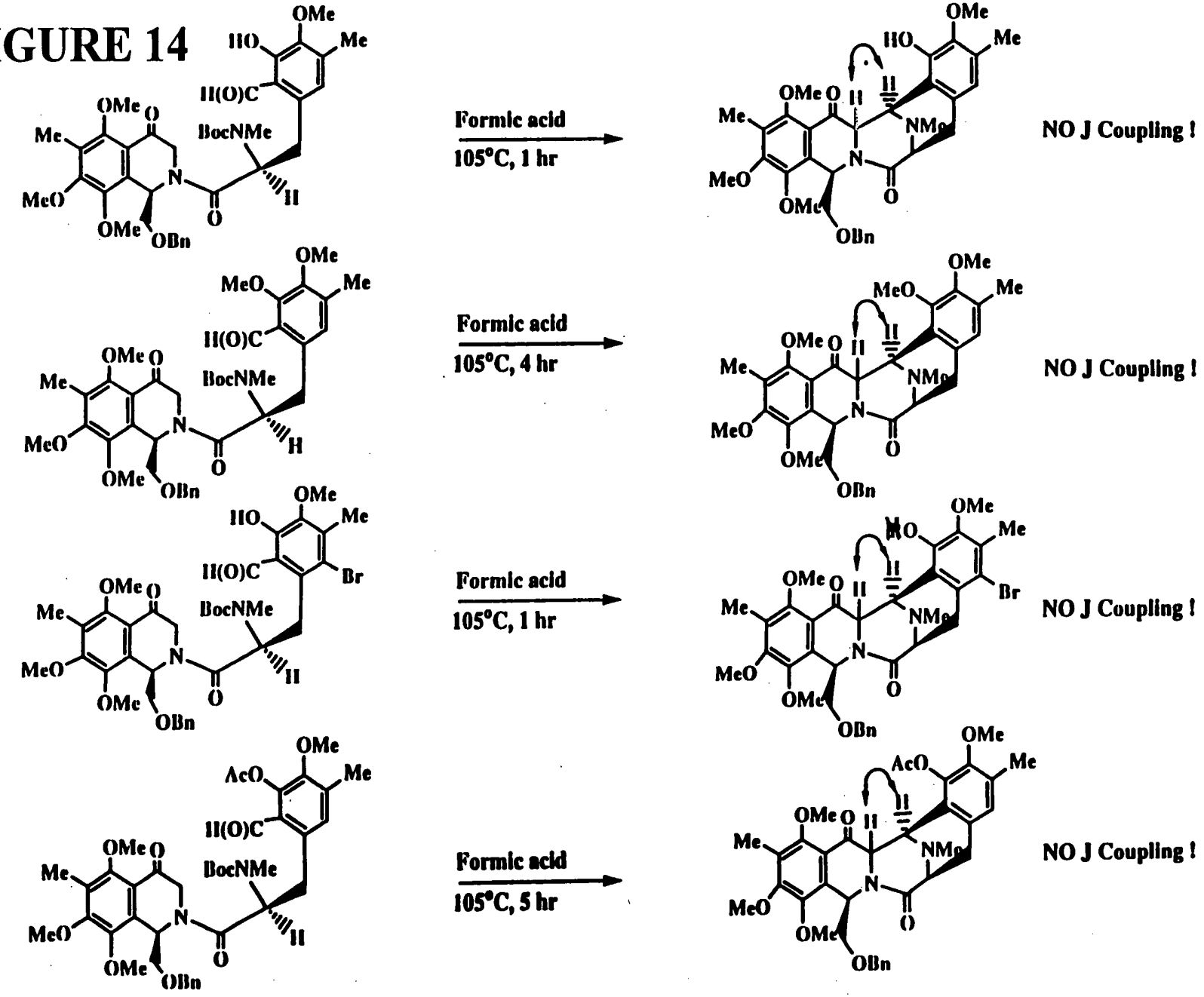

Formic acid
105°C, 1 hr
NO J Coupling !
Formic acid
105°C, 4 hr
NO J Coupling !
Formic acid
105°C, 1 hr
NO J Coupling !
Formic acid
105°C, 5 hr
NO J Coupling !

FIGURE 15